Comparison of predicted and real propofol and remifentanil concentrations in plasma and brain tissue during target-controlled infusion

Anaesthesia 2020, 75, 1626–1634 doi:10.1111/anae.15125

Original Article

Comparison of predicted and real propofol and remifentanil concentrations in plasma and brain tissue during target-controlled infusion: a prospective observational study

L. Van Hese,[1,2] **T. Theys,**[3] **A.R. Absalom,**[4] **S. Rex**[5] and **E. Cuypers**[6,7]

1 PhD student, 5 Associate Professor, Department of Anaesthesiology, University Hospitals Leuven; and Department of Cardiovascular Sciences, KU Leuven, 3000 Leuven, Belgium
6 Professor, Toxicology and Pharmacology Department, KU Leuven, 3000 Leuven, Belgium
2 PhD student, 7 Senior Researcher, Maastricht MultiModal Molecular Imaging (M4I) institute, Division of Imaging Mass Spectrometry, Maastricht University, 6229 ER Maastricht, The Netherlands
3 Associate Professor, Neurosurgery Department, University Hospitals Leuven; Laboratory for Experimental Neurosurgery and Neuroanatomy, Department of Neurosciences, 3000 Leuven, Belgium
4 Professor, Department of Anaesthesiology, University Medical Center Groningen, University of Groningen, The Netherlands

Summary

Target-controlled infusion systems are increasingly used to administer intravenous anaesthetic drugs to achieve a user-specified plasma or effect-site target concentration. While several studies have investigated the ability of the underlying pharmacokinetic-dynamic models to predict plasma concentrations, there are no data on their performance in predicting drug concentrations in the human brain. We assessed the predictive performance of the Marsh propofol model and Minto remifentanil model for plasma and brain tissue concentrations. Plasma samples were obtained during neurosurgery from 38 patients, and brain tissue samples from nine patients. Propofol and remifentanil concentrations were measured using gas chromatography mass spectrometry and liquid chromatography tandem mass spectrometry. Data were analysed from the nine patients in whom both plasma and brain samples were simultaneously obtained. For the Minto model (five patients), the median performance error was 72% for plasma and −14% for brain tissue concentration predictions. The model tended to underestimate plasma remifentanil concentrations, and to overestimate brain tissue remifentanil concentrations. For the Marsh model (five patients), the median prediction errors for plasma and brain tissue concentrations were 12% and 81%, respectively. However, when the data from all blood propofol assays (36 patients) were analysed, the median prediction error was 11%, with overprediction in 15 (42%) patients and underprediction in 21 (58%). These findings confirm earlier reports demonstrating inaccuracy for commonly used pharmacokinetic-dynamic models for plasma concentrations and extend these findings to the prediction of effect-site concentrations.

Correspondence to: E. Cuypers
Email: e.cuypers@maastrichtuniversity.nl
Accepted: 2 May 2020
Keywords: brain concentrations; Marsh propofol model; Minto remifentanil model; target-controlled infusion
This article accompanies an editorial by Irwin et al., Anaesthesia 2020; **75**: 1583–6.

Introduction

When anaesthesia is maintained with inhalational anaesthetic agents, continuous measurement of the end-tidal concentration is routine, and provides a reasonable approximation of arterial drug concentrations and, at steady state, effect-site concentrations. In contrast, when anaesthesia is maintained with intravenous drug infusions, real time analysis of the achieved concentrations is not routinely available. Target-controlled infusion (TCI) systems have been developed to assist with intravenous anaesthetic drug administration [1, 2]. They rely on multi-compartmental pharmacokinetic (PK) models that mathematically describe the processes of distribution and elimination of anaesthetics, to calculate the infusion rates that are necessary to achieve and maintain a user-defined target plasma concentration.

Target-controlled infusion systems are programmed with one or more PK or combined pharmacokinetic and -dynamic (PK/PD) models. The PD component describes the relationship between the concentration in the plasma, the concentration at the site of action of the drug (the so-called effect-site) and the clinical effect. During model development, PD parameters are best estimated from synchronous measurements of the plasma concentration and measures of the clinical effect (usually based on the electro-encephalogram) in the same group of subjects [1]. When TCI systems are programmed with a PK/PD model, this enables an effect-site targeting mode, in which the system calculates and implements the infusion rates required to achieve a user-specified 'target' effect-site concentration. By allowing the anaesthetist to rapidly set and adjust a target concentration aimed at achieving a desired clinical effect, these systems simplify and facilitate intravenous drug titration.

Several models for propofol and remifentanil have been described [3–5]. Among these, the Marsh and Schnider models for propofol and the Minto model for remifentanil are the most commonly used [6, 7]. These PK models provide population estimates of the plasma concentration of these drugs, based on studies in healthy adult volunteers [3–6]. The Schnider and Minto models are combined PK/PD models, whereas the Marsh model was originally only a PK model (the effect-compartment equilibrium rate constant (k_{eo}) from another study was added later) [1]. While the use of TCI systems programmed with these models provides clinically acceptable anaesthesia, the models cannot account for all sources of intra- and inter-individual variability, and so sources of error remain [1]. This has led some investigators to refine these models to make them applicable to a broader population of patients [8, 9].

While the pharmacokinetics of anaesthetic drugs have been extensively studied in humans, almost no information is available for the effect-site, that is, the brain [10, 11]. A limited amount of information is available in animal models. Also in animal models, data on in-vivo pharmacokinetics in the brain are limited. One study developed a PK model for propofol in mice that quantitatively described the propofol distribution into and elimination out of the brain [12]. The predictions were unbiased and the measured brain concentrations approximately equalled the targeted concentrations. However, these data have not been translated to human PK/PD models.

Since multiple known and unknown covariates and confounders were not taken into account during the development of current human PK/PD models, we hypothesised that the predictions of the Minto remifentanil and Marsh propofol models and plasma and brain concentrations will not match well with concentrations measured using the gold standard methods; that is, liquid chromatography tandem mass spectrometry and gas chromatography mass spectrometry. To test this hypothesis, we evaluated the performance of the Marsh and Minto models for the prediction of propofol and remifentanil concentrations in plasma as well as the brains of patients undergoing neurosurgery by comparing TCI with the reference methods.

Methods

This study protocol was approved by the Ethics Committee Research UZ/KU Leuven. Thirty-eight patients were enrolled and provided written informed consent. All were > 18 years and were scheduled to undergo an elective neurosurgical procedure under total intravenous general anaesthesia (using TCI propofol and remifentanil). Patients were included when resection of brain tissue had to be performed in the context of their underlying disease, independent of the current study. While part of the brain tissue was sent to the pathology department for histological examination, the remainder was used for the determination of propofol and remifentanil concentrations. We only analysed brain samples obtained during epilepsy surgery and excluded samples from oncological surgery, since brain tumours might alter cerebral pharmacokinetics of the anaesthetic agents; for example, due to pathologic vascularisation and impairments of the blood–brain barrier [13]. Blood samples were obtained from an arterial line that had been inserted for routine clinical use. All anaesthetic drugs were administered through an intravenous line in the

contralateral arm to that in which the arterial catheter had been placed.

All patients fasted from midnight on the day of surgery. On arrival in the operating theatre, monitoring was initiated with electrocardiography; pulse oximetry; capnography; intra-arterial measurement of blood pressure (IntelliVue MX800 patient monitor, Philips, Boeblingen, Germany) and bispectral index (BIS; Covidien, Dublin, Ireland). An arterial cannula was placed in the radial artery for continuous arterial blood pressure monitoring and frequent blood sampling. Anaesthesia was induced with sufentanil (0.25–0.5 $\mu g.kg^{-1}$ as an intravenous bolus) and propofol by TCI administration. Before tracheal intubation, rocuronium (1 $mg.kg^{-1}$) was administered. General anaesthesia was maintained with TCI infusions of propofol (Diprivan, AstraZeneca, London, UK) and remifentanil (Ultiva, GlaxoSmithKline, Victoria, Australia) using commercially available Alaris PK Syringe infusion pumps (CareFusion UK 305 Ltd, Hampshire, UK). For TCI propofol, the original Marsh model was used, and for remifentanil the Minto model, and the choice of plasma or effect-site target concentrations was at the discretion of the responsible anaesthetist. The anaesthetist was asked to attempt to maintain an equipotent depth of anaesthesia in all patients, by titrating the target concentrations on the basis of clinical signs that may reflect an inadequate depth of anaesthesia (such as sweating, heart rate and blood pressure), while targeting BIS values between 40 and 60, the range recommended by the manufacturer.

A sample of excised brain tissue was retained from 29 patients undergoing brain tumour excision, and from nine undergoing resection of an epileptic focus. Only brain tissue samples originating from epilepsy surgery were further used in this study. The predicted plasma and effect-site propofol and remifentanil concentrations were read off the user interface of the Alaris PK syringe pump and recorded manually at the moment of brain tissue sampling. A single arterial blood sample (4 ml) was obtained at the same time as brain tissue sampling. Brain and blood samples were collected in a sterile polystyrene container and in a tube containing oxalate and EDTA anticoagulants, respectively. To prevent further metabolism of remifentanil by plasma esterases, both samples were immediately frozen at −80°C before assay. Propofol and remifentanil were extracted from whole blood and brain using solid-phase extraction. Analyses of propofol and remifentanil were performed using gas chromatography–mass spectrometry and liquid chromatography tandem mass spectrometry, respectively. Whole blood concentrations were subsequently converted to plasma concentrations using the propofol and remifentanil red blood cell/plasma partition coefficients of 1.13 [14] and 0.89 [15], respectively.

As only a small brain tissue sample per patient was available for this study, four samples were used for remifentanil quantification, four for propofol quantification and one sample was used for both remifentanil and propofol quantification. At the time of brain tissue sampling, the predicted blood and effect-site concentrations had been stable for > 10 min. We assumed a pseudo-steady state, since one can only prove that steady state conditions prevailed if serial blood concentration measurements are available.

One millilitre of whole blood was spiked with 10 µl standard stock solution of deuterated analogues (1 $\mu g.ml^{-1}$) in a conical bottom glass tube. The sample was diluted to 6.0 ml with 0.1 M phosphate buffer pH 6. Brain tissue was first homogenised and weighed and 1 g was transferred to a conical bottom glass tube and diluted to 4.0 ml with 0.1 M phosphate buffer pH 6. This mixture was spiked with 5 µl deuterated stock solution (1 $\mu g.ml^{-1}$). Furthermore, blood and brain tubes were sonicated for 15 min followed by centrifugation for 10 min at 3500 rpm before solid phase extraction. The isolation of analytes was selectively achieved using Mega Bond Elut – Certify cartridges (Agilent Technologies, Diegem, Belgium). Briefly, solid phase extraction columns were first preconditioned and activated with 3 ml MeOH, 3 ml Milli-Q water and 1 ml 0.1 M phosphate buffer pH 6. The sample was loaded on the solid phase extraction cartridge, which was washed with 3 ml of Milli-Q water, 1 ml of acetic acid and 3 ml of MeOH. The solid phase extraction column was then dried for 13 min under vacuum. The analytes were eluted with 3 ml of isopropanol: dichloromethane: ammonium hydroxide (20:78:2). Following solid phase extraction, the eluate was collected and evaporated to dryness under a stream of nitrogen. The residues were reconstituted in 100 µl MeOH:H_2O (30:70) and 5 µl was injected in the liquid chromatography tandem mass spectrometry for the analysis of remifentanil. For propofol analysis, residues were dissolved in 50 µl EtAc where 1 µl was injected in the gas chromatography mass spectrometry system.

Blood and brain concentrations of remifentanil were analysed using a Shimadzu Prominence Ultra-Fast Liquid Chromatograph XR system (Shimadzu Benelux, Jette, Belgium) coupled with 3200 QTRAP mass spectrometry (Sciex, Halle, Belgium). A Kinetex Biphenyl LC column (150 mm × 2.1 mm, 2.6 µm particle size) (Phenomenex, Utrecht, The Netherlands) was used for a chromatographic separation of compounds. The gradient elution phase A

and B consisted of an aqueous buffer pH 8 (10 mM ammonium bicarbonate and ammonium hydroxide) and MeOH. The gradient elution programme applied, started at 30%B; 0–1 min: 30–55%B; 1–7 min: 90%B; 8–8.5 min: 90–30%B. The total analytical run time was 10 min. Flow rate, column oven and sample injection were 0.5 $ml.min^{-1}$, 45°C and 5 μl, respectively. The mass spectrometer was operated in multiple reaction monitoring mode and a Turbo V electrospray ionisation source was used in positive mode. Quantification was performed using multiple-reaction monitoring of the transitions of m/z 377.2 → 113.1 for remifentanil and m/z 242.2 → 129.0 for IS, with a dwell time of 15 ms. Source-dependent parameters were set as follows: curtain gas: nitrogen, 10 psi; nebulising gas: nitrogen, 50 psi; heater gas: nitrogen, 50 psi; ion source temperature: 600°C; and ion source voltage: 5500 V. Blood and brain concentrations of propofol were analysed using a 5977B gas chromatography instrument, combined with 7890B mass spectrometer equipped with electron ionisation and quadrupole analyser (Agilent technologies, Palo Alto, CA, USA). Separation was performed using a DB-5ms MS capillary column (30 m × 0.25 mm ID, film thickness 0.25 μm, Agilent). A pulsed split injected mode was employed, at 250°C. Oven temperature was held at 80°C for 3 min, increased at 30°C.min^{-1} up to 300°C. The ion source and interface temperatures were set at 230°C and 250°C, respectively. The propofol and propofol-D17 solution were detected using molecular ions at m/z 163 and 177, respectively.

The measured plasma and brain tissue concentrations of remifentanil and propofol were compared with the concentrations estimated by the TCI pump. The prediction error was defined as the difference between the measured and predicted concentrations for each individual patient. For each subject the performance error was calculated as follows:

Performance error (%) = $[(C_{meas} - C_{pred})/(C_{pred})] \times 100$, with C_{pred} being the predicted plasma or brain tissue drug concentration and C_{meas} the measured blood or brain tissue concentration in that sample.

Statistical analyses were conducted using IBM SPSS statistics (version 25.0, IBM Corp., Armonk, NY, USA) or using GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA, USA). Tests of normality were measured with the Shapiro-Wilk test.

Results

We included 38 adult neurosurgical patients (20 men and 18 women), nine of whom underwent epilepsy surgery. Online Table S1 shows the demographic data of all 38 patients from whom blood or brain tissue samples were obtained. Mean (SD) age was 53 (17) y and BMI 25.8 (4.7) $kg.m^{-2}$ For patients in whom both a blood and brain tissue sample were available, the measured and predicted plasma and effect-site concentrations of propofol and remifentanil are presented in Table 1. An overview of the measured and predicted remifentanil and propofol concentrations and the corresponding performance errors from all patients can be found in online Table S1.

Remifentanil concentrations

Brain and plasma samples from five patients were analysed. The measured remifentanil concentrations in the brain ranged from 1.29 $ng.ml^{-1}$ to 8.89 $ng.ml^{-1}$. However, in these patients, plasma concentrations ranged from 5.53 $ng.ml^{-1}$ to 20.01 $ng.ml^{-1}$. The error between the measured concentrations and the Minto model predictions ranged from −3.21 $ng.ml^{-1}$ to 3.89 $ng.ml^{-1}$ in the brain and from 1.03 $ng.ml^{-1}$ to 14.01 $ng.ml^{-1}$ in plasma. The model demonstrated a median performance error of −14% and a median absolute performance error of 22% in the brain. In plasma, the median performance error and the median absolute performance error were 72% (Table 2). In contrast to plasma concentrations, the Minto model tended to overestimate brain concentrations (Fig. 1).

Propofol concentrations

Brain tissue and plasma concentration data were available from five patients. Measured brain and plasma concentrations ranged from 5.64 $\mu g.ml^{-1}$ to 7.68 $\mu g.ml^{-1}$ and from 2.74 $\mu g.ml^{-1}$ to 14.71 $\mu g.ml^{-1}$, respectively. The median error was 2.99 $\mu g.ml^{-1}$ in the brain and 0.55 $\mu g.ml^{-1}$ in plasma. The median performance error and median absolute performance error were 81% for the brain concentrations, and for plasma concentrations the median performance error and absolute performance error were 12% and 18% for the Marsh model (Table 2). The Marsh model thus tended to underestimate propofol concentrations both in plasma and the brain (Fig. 1). However, when the plasma propofol concentrations of all 36 patients are analysed, the Marsh model underestimated propofol plasma concentrations in 21 (58%) patients and overestimated propofol concentrations in 15 (42%) patients (online Table S1). The median performance error in all patients was 11% and the median absolute performance error was 39% in plasma. The literature overview, shown in Figure 2, further confirms this inaccuracy as some studies report under-prediction and others report over-prediction with the Marsh model.

Table 1 Baseline characteristics and anaesthesia-related data of patients in whom both a blood and brain tissue sample were available.

					Remifentanil				Propofol			
					Plasma		Brain		Plasma		Brain	
Age; y	Sex	Weight; kg	Height; m	BMI; kg. m^2	C_{meas} (ng.ml^{-1})	C_{pred} (ng.ml^{-1})	C_{meas} (ng.g^{-1})	C_{pred} (ng.ml^{-1})	C_{meas} (µg.ml^{-1})	C_{pred} (µg.ml^{-1})	C_{meas} (µg.g^{-1})	C_{pred} (µg.ml^{-1})
66	M	67	1.72	22.65	8.54	5.00	8.89	5.00				
60	M	91	1.73	30.41	20.01	6.00	5.39	6.00				
41	F	87.5	1.66	31.75					5.05	4.50	7.11	4.50
38	M	92	1.78	29.04	10.33	6.00	5.17	6.00	14.71	4.00	5.64	4.00
65	M	74	1.79	23.10	10.86	6.00	4.68	6.00				
51	M	74.8	1.81	22.83	5.52	4.50	1.29	4.50				
50	F	72	1.72	24.34					4.36	3.70	6.69	3.70
38	F	89	1.63	33.50					2.74	4.00	7.50	4.00
66	F	58	1.67	20.80					4.23	3.80	7.68	3.80

C_{meas}, measured concentration; C_{pred}, predicted concentration.

Discussion

Although TCI administration of propofol and remifentanil using the Marsh and Minto models allows clinically safe and stable conduct of anaesthesia, we observed significant inaccuracy in both plasma and brain concentration predictions of these models. The Minto pharmacokinetic parameter set resulted in an underprediction of the plasma remifentanil concentrations by 72% and an overprediction of brain tissue remifentanil by 14%. Furthermore, the Marsh model showed an overall underprediction in both plasma and the brain by 12% and 81%, respectively, meaning that the measured brain tissue concentration was 81% higher than the effect-site concentration predicted by the Marsh model.

Table 2 Performance errors (PE) and biases of the individual patients for propofol and remifentanil TCI in plasma and the brain. Bispectral index (BIS) at the moment of sampling (median BIS over the 10 min before sampling – median BIS over the 10 min after sampling)

Remifentanil										
Plasma					**Brain**					
C_{meas} (ng.ml^{-1})	C_{pred} (ng.ml^{-1})	PE (%)	Abs(PE) (%)	Error (ng.ml^{-1})	C_{meas} (ng.g^{-1})	C_{pred} (ng.ml^{-1})	PE (%)	Abs(PE) (%)	Error (ng.ml^{-1})	BIS
8.54	5	70.7	70.7	3.5	8.89	5	77.8	77.8	3.89	40 (44-42)
20.01	6	233.5	233.5	14.0	5.39	6	-10.2	10.2	-0.61	43 (41-40)
10.33	6	72.2	72.2	4.3	5.17	6	-13.8	13.8	-0.83	39 (35-42)
10.86	6	81.0	81.0	4.9	4.68	6	-22.0	22.0	-1.32	37 (39-37)
5.52	4.50	22.7	22.7	1.0	1.29	4.5	-71.3	71.3	-3.21	40 (39-45)
Propofol										
Plasma					**Brain**					
C_{meas} (µg.ml^{-1})	C_{pred} (µg.ml^{-1}	PE (%)	bs(PE) (%)	Error (µg.ml^{-1})	meas (µg.g^{-1})	Cpred (µg.ml^{-1})	PE (%)	bs(PE) (%)	Error (µg.ml^{-1})	BIS
5.05	4.5	12.2	12.2	0.6	7.11	4.5	58.0	58.0	2.6	28 (24-31)
14.71	4	267.8	267.8	10.7	5.64	4	41.0	41.0	1.6	39 (35-42)
4.36	3.7	17.8	17.8	0.7	6.69	3.7	80.8	80.8	3.0	39 (40-40)
2.74	4	-31.5	31.5	-1.3	7.5	4	87.5	87.5	3.5	No BIS
4.23	3.8	11.3	11.3	0.4	7.68	3.8	102.1	102.1	3.9	No BIS

C_{meas}, measured concentration; C_{pred}, predicted concentration.

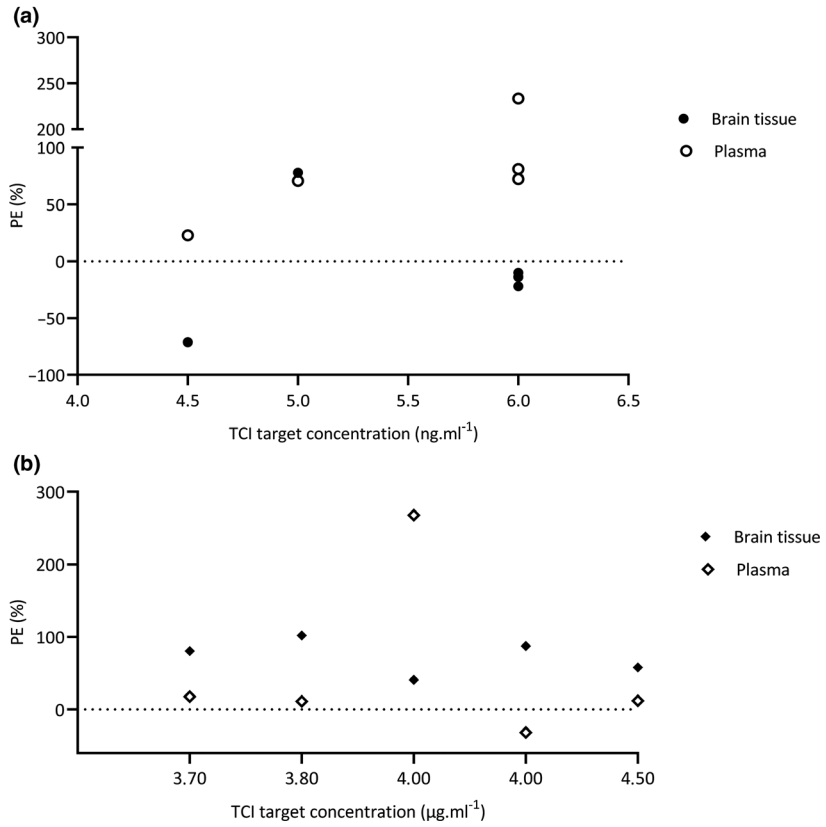

Figure 1 Relation between the performance error (PE) and the target concentrations in plasma and the brain. (a) Predicted TCI target concentrations of remifentanil were calculated using the pharmacokinetic parameter sets of Minto. Remifentanil plasma concentration (open circle); remifentanil effect-site concentrations (filled circle). (b) Predicted TCI target concentrations of propofol were calculated using the pharmacokinetic parameter sets of Marsh. Propofol plasma concentrations (open diamond); propofol effect-site concentrations (filled diamond)

Up until now, the Marsh and Minto pharmacokinetic models for propofol and remifentanil have not been assessed for the accuracy of the effect-site or brain concentration predictions. Instead, validation of these models has always been done by measuring plasma concentrations under steady state conditions and assuming that, under these conditions, plasma and effect-site concentrations have equilibrated. However, it is possible that this assumption is not true, since most drugs used in anaesthesia have very different solubility in fat and water or plasma, and some drugs may or may not be actively transported into or out of the brain, meaning that at steady state situations, the concentration in the plasma and in the effect-site may be different.

So far, the assumption of equivalence of plasma and effect-site concentrations at steady state has not been investigated in humans. Our data suggest that this assumption is false. but do not provide definitive proof, since we have not demonstrated that plasma concentrations were at or close to steady state at the time of brain tissue sampling. It is noteworthy that, in the case of propofol which is insoluble in water and highly fat soluble, in five out of five patients the concentration was considerably higher in the brain than in the plasma. On the other hand, for remifentanil which is water soluble and only modestly fat soluble, the plasma concentration was higher than the brain concentration in four out of five patients.

The distribution of propofol in the brain has only been studied in animals [12, 16]. On the other hand, some work has been done to understand the relationship among free and total propofol concentrations in the blood and in the human cerebrospinal fluid (CSF) as a means of understanding the uptake of propofol by the brain. Propofol binds strongly to plasma proteins and red blood cells [17], which are among the reasons why unbound plasma concentrations are usually of the order of 1% [18]. Nevertheless, Dutta et al. showed in rats that not only unbound drug, but also drug bound to plasma proteins and blood cells can participate in the uptake and transfer of propofol to its effect-site [16]. Indeed, it was found that at

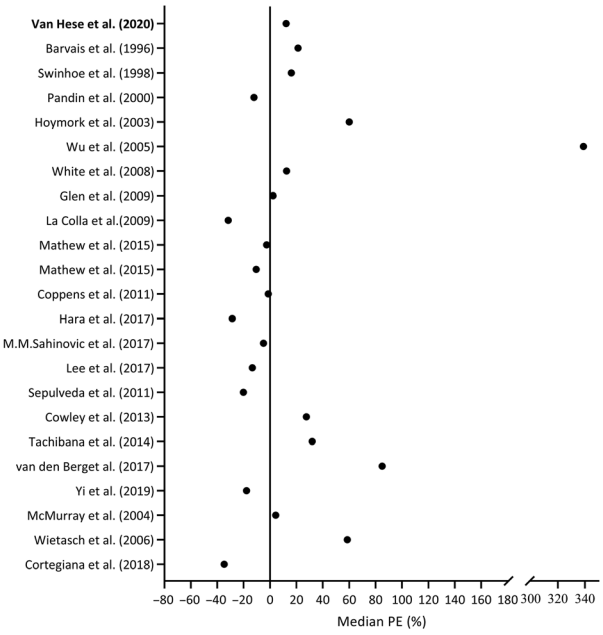

Figure 2 Literature overview of studies investigating the performance error (PE) of the Marsh pharmacokinetic model for propofol TCI to predict plasma concentrations. Circles represent the median PE.

equilibrium, although the total plasma propofol concentration was almost two orders of magnitude higher than the total concentration in the CSF, the unbound propofol concentration in the CSF was significantly higher than the unbound propofol concentration in the plasma [18]. The binding of propofol to molecules and cells in the CSF may, thus, increase the propofol concentration in the CSF and lead to shortening of propofol transit time into the CSF [18]. The unbound drug concentration in plasma can, therefore, not be directly related to its concentrations in the brain. It is interesting to note that in four out of the five patients in our study in whom plasma and brain tissue propofol concentrations were measured, the brain tissue concentrations were higher than the plasma concentrations (Table 1). In conclusion, it should not be taken for granted that the Cp and Ce are always similar during steady-state anaesthesia. This may partly explain the significantly higher underestimation of propofol concentrations that we found in the brain compared with the plasma.

As shown in Figure 2, the literature shows inconclusive results regarding under- or over-prediction of plasma propofol concentrations with the Marsh model [19–25].These conflicting results can be partly attributed to the varied cohorts of patients investigated, to the associated differences in distribution/redistribution and/or elimination, and to how the plasma concentrations were measured. It has been demonstrated that coexisting conditions like obesity or sarcopenia have a great impact on the Marsh model performance [23, 26, 27]. The differences in estimated clearance in this population compared with the normal weight reference population might explain these discrepancies.

Furthermore, pharmacokinetic interactions, due to co-administration of other drugs with propofol, may explain the poor model performance. Propofol in this study was used in combination with remifentanil. Mertens et al. studied the predictive performance of the Minto model when used for TCI remifentanil administration during propofol anaesthesia in surgical patients. Their study demonstrated an overprediction of the measured remifentanil plasma concentration by 15%, although there was no significant correlation between blood propofol concentrations and the performance error of remifentanil [28]. On the other hand, Wietasch et al. found that, when remifentanil and propofol were combined, the Marsh PK parameter set systematically underestimated propofol plasma concentrations [24].

For TCI remifentanil administration using the Minto model, we found an underestimation of remifentanil concentration in plasma but an overestimation in the brain. The overestimation of the brain concentration by the Minto model may be attributable to hydrolysis by non-specific blood and tissue esterases, resulting in the formation of the carboxylic acid metabolite, GI-90291. Hydrolysis of remifentanil in blood and by liver and kidneys was very low in male Beagle dogs, whereas muscle, intestine and brain had the highest extraction ratios [29]. The hydrolysis in tissue, for example, the brain, might, therefore, be more likely to determine the rapid metabolism of remifentanil.

Our study has several limitations. First, only one blood and brain sample was analysed in each patient to measure the propofol and remifentanil concentrations. Brain sample resection was performed in the context of the patients' underlying disease. The progress of the surgical resection procedure determined the time-point at which a brain tissue sample was obtained and, therefore, also the timing of blood sampling. As a result, sampling was not done at a fixed time during surgery, and neither was it possible to perform it at a fixed time period of the start of the remifentanil and propofol infusions. Secondly, anaesthesia was maintained with a combination of propofol and remifentanil, drugs known to interact pharmacokinetically with each other. Furthermore, patients undergoing neurosurgery commonly receive other drugs, such as anti-epileptic drugs, and sometimes steroid, and these categories of drugs can also have pharmacokinetic interactions with propofol and remifentanil. Finally, the

number of brain samples was limited. Only nine brain tissue samples were available for analysis.

Further work is required, and in particular, brain samples are needed under steady state plasma concentrations. If the above findings are replicated, then the current assumptions inherent in PK/PD models will require revision, as will the techniques for estimation of the k_{eo}. For example, one method of estimating the k_{eo} is to intermittently measure plasma concentrations and use a processed electroencephalogram monitor to continuously assess clinical effect after a bolus dose. A hysteresis loop of the relationship between plasma concentration and clinical effect can then be drawn, and mathematical optimisation techniques are used to estimate a sigmoid relationship between clinical effect and an effect-site concentration, thereby 'collapsing the loop'. If the assumption mentioned above is false, then an alternative technique to a simple 'collapsing the loop' technique will be required, involving a peak effect-site concentration greater than that at the moment of maximal effect, possibly resulting in a better understanding of the relationship between plasma concentrations, effect-site concentrations and clinical effect.

In conclusion, this study is the first to compare propofol and remifentanil plasma and brain concentrations, giving insight into the accuracy of TCI pharmacokinetic models in the brain. The main result of our study was that the Minto model showed significant underestimation of remifentanil plasma concentrations but tended to overestimate brain concentrations. The Marsh model showed an overall underestimation of propofol concentrations that was higher in the brain compared with plasma. These conflicting results show that effect-site concentrations of anaesthetic drugs during equilibrium cannot be assumed to be equal to the plasma concentration. More studies are needed to confirm these results on a larger scale and investigate the associated clinical effects for the patient.

Acknowledgements

This work was made possible with the financial support of the FWO Research Foundation, Belgium and the Clinical Research and Education Council (KOOR) of UZ Leuven, Belgium. The authors are indebted to the invaluable help and support of our study co-ordinator, C. Huygens. No other external funding or competing interests declared.

References

1. Absalom AR, Glen JIB, Zwart GJC, Schnider TW, Struys MMRF. Target-controlled infusion: a mature technology. *Anesthesia and Analgesia* 2016; **122**: 70–8.
2. Struys MMRF, De Smet T, Glen JIB, Vereecke HEM, Absalom AR, Schnider TW. The history of target-controlled infusion. *Anesthesia and Analgesia* 2016; **122**: 56–69.
3. Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia* 1991; **67**: 41–8.
4. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170–82.
5. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502–16.
6. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33.
7. Nimmo AF, Absalom AR, Bagshaw O, et al. Guidelines for the safe practice of total intravenous anaesthesia (TIVA). *Anaesthesia* 2019; **74**: 211–24.
8. Eleveld DJ, Colin P, Absalom AR, Struys MMRF. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *British Journal of Anaesthesia* 2018; **120**: 942–59.
9. Eleveld DJ, Proost JH, Vereecke H, et al. An allometric model of remifentanil pharmacokinetics and pharmacodynamics. *Anesthesiology* 2017; **126**: 1005–18.
10. Wakeling HG, Zimmerman JB, Howell S, Glass PS. Targeting effect compartment or central compartment concentration of propofol : what predicts loss of consciousness? *Anesthesiology* 1999; **90**: 92–7.
11. Kazama T, Ikeda K, Morita K, et al. Comparison of the effect-site keos of propofol for blood pressure and EEG bispectral index in elderly and younger patients. *Anesthesiology* 1999; **90**: 1517–27.
12. Shortal BP, Reitz SL, Aggarwal A, et al. Development and validation of brain target controlled infusion of propofol in mice. *PLoS One* 2018; **13**: e0194949.
13. Sahinovic MM, Eleveld DJ, Miyabe-Nishiwaki T, Struys MMRF, Absalom AR. Pharmacokinetics and pharmacodynamics of propofol: changes in patients with frontal brain tumours. *British Journal of Anaesthesia* 2017; **118**: 901–9.
14. Weaver BMQ, Staddon GE, Raptopoulos D,Mapleso WW. Partitioning of propofol between blood cells, plasma and deproteinised plasma in sheep. *Proceedings of the Association of Veterinary Anaesthetists* 1998; **25**: 19–23.
15. Kabbaj M, Vachon P, Varin F. Impact of peripheral elimination on the concentration–effect relationship of remifentanil in anaesthetized dogs. *British Journal of Anaesthesia* 2005; **94**: 357–65.
16. Dutta S, Matsumoto Y, Muramatsu A, Matsumoto M, Fukuoka M, Ebling WF. Steady-state propofol brain:plasma and brain: blood partition coefficients and the effect-site equilibration paradox. *British Journal of Anaesthesia* 1998; **81**: 422–4.
17. Dawidowicz AL, Kalitynski R, Nestorowicz A, Fijalkowska A. Changes of propofol concentration in cerebrospinal fluid during continuous infusion. *Anesthesia and Analgesia* 2002; **95**: 1282–4.
18. Dawidowicz AL, Kalitynski R, Fijalkowska A. Free and bound propofol concentrations in human cerebrospinal fluid. *British Journal of Clinical Pharmacology* 2003; **56**: 545–50.
19. Høymork SC, Ræder J, Grimsmo B, Steen PA. Bispectral index, predicted and measured drug levels of target-controlled infusions of remifentanil and propofol during laparoscopic cholecystectomy and emergence. *Acta Anaesthesiologica Scandinavica* 2000; **44**: 1138–44.
20. Wu J, Zhu SM, He HL, Weng XC, Huang SQ, Chen YZ. Plasma propofol concentrations during orthotopic liver transplantation. *Acta Anaesthesiologica Scandinavica* 2005; **49**: 804–10.
21. van den Berg JP, Vereecke HEM, Proost JH, et al. Pharmacokinetic and pharmacodynamic interactions in

anaesthesia. A review of current knowledge and how it can be used to optimize anaesthetic drug administration. *British Journal of Anaesthesia* 2017; **118**: 44–57.
22. Cortegiani A, Pavan A, Azzeri F, Accurso G, Vitale F, Gregoretti C. Precision and Bias of Target-Controlled Prolonged Propofol Infusion for General Anesthesia and Sedation in Neurosurgical Patients. *Journal of Clinical Pharmacology* 2018; **58**: 606–12.
23. La Colla L, Albertin A, La Colla G, et al. No adjustment vs. adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. *European Journal of Anaesthesiology* 2009; **26**: 362–9.
24. Wietasch JKG, Scholz M, Zinserling J, et al. The performance of a target-controlled infusion of propofol in combination with remifentanil: a clinical investigation with two propofol formulations. *Anesthesia and Analgesia* 2006; **102**: 430–7.
25. Hara M, Masui K, Eleveld DJ, Struys MMRF, Uchida O. Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anaesthesia. *British Journal of Anaesthesia* 2017; **118**: 415–23.
26. Yi J-M, Doh I, Lee S-H, et al. Predictive performance of a new pharmacokinetic model for propofol in underweight patients during target-controlled infusion. *Acta Anaesthesiologica Scandinavica* 2019; **63**: 448–54.
27. Lee YH, Choi GH, Jung KW, et al. Predictive performance of the modified Marsh and Schnider models for propofol in underweight patients undergoing general anaesthesia using target-controlled infusion. *British Journal of Anaesthesia* 2017; **118**: 883–91.
28. Mertens MJ, Engbers FHM, Burm AGL, Vuyk J. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. *British Journal of Anaesthesia* 2003; **90**: 132–41.
29. Chism JP, Rickert DE. The pharmacokinetics and extra-hepatic clearance of remifentanil, a short acting opioid agonist, in male beagle dogs during constant rate infusions. *Drug Metabolism and Disposition* 1996; **24**: 34 LP–40.

Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Demographic data, performance error, measured and predicted plasma and brain propofol and remifentanil concentrations of all patients investigated.